IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **YANG *et al.***	Confirmation No.: 1982
Appl. No.: **09/677,574**	Art Unit: 1652
Filed: **October 3, 2000**	Examiner: Hutson, R.
For: **High Fidelity Polymerases and Uses Thereof**	Atty. Docket: IVGN 195.1 CON

Brief on Appeal Under 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed June 4, 2007, Appellants hereby file a revised Appeal Brief. This revised Appeal Brief has been corrected to include the signature of Appellants' agent of record.

It is not believed that extensions of time or fees are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore are hereby authorized to be charged to Deposit Account No. 50-3994.

Table of Contents

I. Real Party In Interest

The real party in interest in this appeal is Invitrogen Corporation.

II. Related Appeals and Interferences

No other prior or pending appeals, interferences or judicial proceedings are known to the Appellants or the Appellants' legal representative who may be related to, or directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 are pending in the application.

Claims 1, 3-5, 10-13, 15-16, 18-19, 21-36, 41-68, 70, and 76-82 have been canceled.

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 are rejected.

IV. Status of Amendments

No amendments were filed subsequent to the final rejection.

V. Summary of Claimed Subject Matter

Claim 2 is the sole independent claim involved in this Appeal. The invention defined by claim 2 relates generally to Pol I type *Thermatoga neapolitana* DNA polymerase comprising a modification that reduces or eliminates misincorporation of

nucleotides during nucleic acid synthesis. The claimed DNA polymerases comprise modifications **(1)** at amino acids Arg 722 and Lys 726 or **(2)** at amino acids Arg 722 and Phe 730. Support for claim 2 can be found throughout the Specification, for example, at page 5, line 26 through page 6, line 8; page 19, lines 4-28; page 20, lines 1-9 and the table; *See* Specification page 21, table; page 24, lines 1-9; pages 46-47, Example 14; and page 48, Example 17.

VI. Grounds of Rejection to be Reviewed on Appeal

There is only one ground of rejection to be reviewed on appeal:

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 stand rejected as being non-compliant with the Written Description Requirement of 35 U.S.C. § 112, first paragraph.

VII. Argument

A. The Legal Standard for Written Description

In order to satisfy the written description requirement, the patent specification must provide an adequate "written description of the invention, and of the manner and process of using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art … to make and use the same." 35 U.S.C. § 112, first paragraph.

The Board of Patent Appeals of the United States Patent Office has held that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention . . . . the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under

the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 U.S.P.Q.2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification . . . ." *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996).

A patent applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112. (*see Parks* and *Alton*). Rather, subject matter that "might fairly be deduced from the original application" is considered to be described in the application as filed. *Acme Highway Products Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080, 167 U.S.P.Q. 129, 133 (6th Cir. 1970) (citations omitted), *cert. denied*, 401 U.S. 956, 91 S.Ct. 977, 28 L.Ed.2d 239, 168 U.S.P.Q. 737 (1971), *followed by Westphal v. Fawzi*, 666 F.2d 575, 577, 212 U.S.P.Q. 321, 322-323 (C.C.P.A. 1981). Moreover, the Federal Circuit has held that:

> [a] description of a genus of [molecules] may be achieved by means of a recitation of a representative number of [molecules], defined by nucleotide sequence, falling within the scope of the genus . . . .

Regents of Univ. of Calif. v. Eli Lilly & Co., 119 F.3d 1559, 1569, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997).

The Federal Circuit has also provided additional tests subsequent to *Eli Lilly* for satisfying the written description requirement. For example the court has held that functional descriptions of biological material can satisfy the written description requirement if a structure/function correlation is known in the art. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1332, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003). ("*Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." (citation omitted)). The Federal Circuit has also reasoned, in reference to the recitation of known biological materials, that a description of a genus by words alone is sufficient to satisfy the written description requirement. *Id.* The Federal Circuit has even acknowledged that a specification may adequately describe a genus even though it fails to describe a *single species* falling within the genus. *See Eli Lilly,* 119 F.3d at 1569, 43 U.S.P.Q.2d at 1406.

B. The Examiner's Position

The outstanding Written Description rejection is based on the Examiner's assertions that Appellants' Specification does not provide support for Pol I type *Thermatoga neapolitana* DNA polymerases comprising modifications at amino acids Arg 722 and Lys 726 or at amino acids Arg 722 and Phe 730. Specifically, the Examiner has stated that:

> "*support for the claimed genus of mutations are not supported by the recited species (i.e., Phe730 is not supported by applicants recited species of F730A and F730Y).*"

See Office Action dated July 11, 2006 at page 3.

C. The Appellants' Position

Claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 are fully supported by Appellants' Specification, which is compliant with the Written Description Requirement of 35 U.S.C. § 112, first paragraph.

The claims relate to *Thermatoga neapolitana* (*Tne*) DNA polymerases modified to reduce or eliminate nucleotide misincorporation during nucleic acid synthesis. The claimed DNA polymerases comprise substitutions at amino acids Arg722 and Lys726 (**Arg722/Lys726 mutants**) or at amino acids Arg722 and Phe730 (**Arg722/Phe730 mutants**). The claimed Arg722/Lys726 mutants have an amino acid substitution at position Arg722 (*i.e.*, with Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val) and an amino acid substitution at position Lys726 (*i.e.*, with Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val). Likewise, the claimed Arg722/Phe730 mutants have an amino acid substitution at position Arg722 (*i.e.*, with Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, or Val) and an amino acid substitution at position Phe730 (*i.e.*, with Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr, or Val).

1. Arg722 and Lys726 Mutants

Appellants' Specification clearly discloses Arg722/Lys726 mutant *Tne* DNA polymerases. The Specification discloses that mutations at positions Arg, Lys, Phe and/or Tyr of a DNA polymerase O-helix can reduce nucleotide misincorporation. *See* Specification at page 19, lines 9-16 and page 5, lines 25-28. Specifically, mutations at O-helix positions Arg722 and/or Lys726 in *Tne* are identified as reducing nucleotide misincorporation. *See* Specification page 20, lines 1-9 and page 21, table at lines 1-10. The Specification indicates that Arg722 of *Tne* may be substituted with any other amino acid including Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. *See* Specification page 19, lines 17-22 and page 20, lines 1-9 and the table at line 20. Similarly, the Specification indicates that Lys726 of *Tne* amino acid may be substituted with any other amino acid including Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. *See* Specification page 19, lines 23-28 and page 20, lines 1-9 and the table at line 20.

Considering the aspects of Appellant's Specification referenced above, it is clear that those skilled in the art would have recognized that the present inventors had indeed invented the claimed Arg722/Lys726 modified *Tne* DNA polymerases.

2. Arg722 and Phe730 Mutants

Appellants' Specification clearly discloses the claimed Arg722/Phe730 mutant *Tne* DNA polymerases. The Specification discloses that, in addition to the substitutions described immediately above for reducing nucleotide misincorporation, mutant

polymerases may contain other modifications. Specifically, the Specification indicates that mutant DNA polymerases may also include mutations that reduce discrimination against dideoxynucleotides. *See* Specification page 21, lines 15-23. As the Specification states, "…other functional changes may be made to the polymerase having increased fidelity. For example, the polymerase may also be modified to … reduce discrimination against ddNTPs." *See* Specification page 6, lines 5-8. The Specification discloses that mutations at Phe within the DNA polymerase O-helix reduce discrimination against dideoxynucleotides. *See* Specification page 23, lines 20-25. The Specification goes on to specifically disclose *Tne* DNA polymerases having Arg722 and Phe730 mutations. *See* Specification page 51, table. The Specification indicates that Arg722 of *Tne* may be substituted with any other amino acid including Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val. *See* Specification page 19, lines 17-22 and page 20, table at line 20. Similarly, the Specification indicates that amino acid Phe730 may be substituted with any other amino acid including Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr, and Val. *See* Specification page 24, lines 1-5. Furthermore, the Specification discloses at least six working examples of such Arg722/F730 double mutants of the *Tne* DNA polymerase (including various Arg722 substitutions combined with F730A or F730Y substitutions). *See* Specification Example 14 on page 46 and Example 17 on page 17.

Considering the aspects of Appellant's Specification referenced above, it is clear that those skilled in the art would have recognized that the present inventors had indeed invented the claimed Arg722/Phe730 modified *Tne* DNA polymerases.

D. Conclusion

In view of the forgoing discussion, Appellants respectfully submit that claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 are fully supported by the Specification, which is compliant with the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, Appellants respectfully request that the Board reverse the Examiner's final rejection of claims 2, 6-9, 14, 17, 20, 37-40, 69 and 71-75 under 35 U.S.C. § 112, and that the Board remand this application for issuance.

Respectfully submitted,

INVITROGEN CORPORATION

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Date: June 18, 2007

VIII. Claims Appendix

Claim 2. A Pol I type *Thermatoga neapolitana* DNA polymerase comprising a modification that reduces or eliminates misincorporation of nucleotides during nucleic acid synthesis, wherein said modification comprises:

amino acid position Arg722 of said *Thermotoga neapolitana* polymerase substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val and amino acid position Lys726 of a *Thermotoga neapolitana* polymerase substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val, or

amino acid position Arg722 of a *Thermotoga neapolitana* polymerase substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val and amino acid position Phe730 of said *Thermotoga neapolitana* polymerase substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr, and Val.

Claim 6. The polymerase of claim 2, further comprising one or more modifications to reduce or eliminate one or more activities selected from the group consisting of:

(a) the 3′→5′ exonuclease activity of the polymerase;

(b) the 5′→3′ exonuclease activity of the polymerase; and

(c) the discriminatory activity against one or more dideoxynucleotides.

Claim 7. The polymerase of claim 2, wherein said polymerase is modified to reduce or eliminate 3′→5′ exonuclease activity.

Claim 8. The polymerase of claim 2, wherein said polymerase is modified to reduce or eliminate discriminatory activity against one or more dideoxynucleotides.

Claim 9. The polymerase of claim 2, wherein said polymerase is modified to reduce or eliminate 5′→3′ exonuclease activity.

Claim 14. The polymerase of claim 2, wherein Arg722 is substituted with an amino acid selected from the group consisting of Asn, Asp, Cys, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Ser, Thr, Tyr and Val.

Claim 17. The polymerase of claim 2, wherein Lys726 is substituted with an amino acid selected from the group consisting of Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

Claim 20. The polymerase of claim 2, wherein Arg722 is substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val, and wherein Lys726 is substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

Claim 37. A kit for amplifying, synthesizing, or sequencing a DNA molecule comprising one or more of the modified polymerases of claim 2.

Claim 38. The kit of claim 37, further comprising one or more dideoxyribonucleoside triphosphates.

Claim 39. The kit of claim 37, further comprising one or more deoxyribonucleoside triphosphates.

Claim 40. The kit of claim 38, further comprising one or more deoxyribonucleoside triphosphates.

Claim 69. The polymerase of claim 14, wherein Arg722 is substituted with an amino acid selected from the group consisting of Lys, His, Asn, Tyr, and Leu.

Claim 71. The polymerase of claim 2, wherein Arg722 is substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val, and Phe730 is substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Pro, Ser, Thr, Trp, Tyr and Val.

Claim 72. The polymerase of claim 71, wherein Arg722 is substituted with an amino acid selected from the group consisting of Lys, Gln, His, Asn, Tyr, and Leu.

Claim 73. The polymerase of claim 71, wherein Phe730 is substituted with Tyr.

Claim 74. The polymerase of claim 71, wherein Arg722 is substituted with an amino acid selected from the group consisting of Lys, Gln, His, Asn, Tyr, and Leu, and Phe730 is substituted with Tyr.

Claim 75. The polymerase of claim 17, wherein Lys726 is substituted with Arg.

IX. Evidence Appendix

None.

X. Related Proceedings Appendix

None.